## REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the following arguments, literature references and legal analysis.

### *Specification Amendment*

The specification has been amended to insert after the title and before the first line of the specification, the priority history of this Application. This priority was claimed in the inventor's Declaration as filed and was acknowledged in the official Filing Receipt. Moreover, a certified copy of priority application GB 0316127.0 is present in the US Patent and Trademark Office PAIR electronic file for this application. It is therefore respectfully requested that in the next Office Action Summary, the Examiner acknowledge the claim for priority and that a certified copies of the priority document has been received.

### *Claim Status and Summary*

The claims have not been amended herein. Therefore, claims 3, 4, 7, 8 and 15 remain pending and under rejection.

The presently claimed invention relates to a novel and particularly advantageous combination therapy for the treatment of cancer:

- The method of independent claim 3 is directed toward the *double* combination comprising the administration of
    - an effective amount of AZD2171 (an inhibitor of VEGFR) before, after or simultaneously with
    - an effective amount of ZD1839 (an inhibitor of EGFR).
- The method of independent claim 4 is directed toward the *triple* combination comprising administration of
    - an effective amount of AZD2171 before, after or simultaneously with
    - an effective amount of ZD1839, and before, after or simultaneously with
    - an effective amount of ionising radiation.

As will be demonstrated hereinafter, the cited and applied prior art, when properly considered as a whole and in context of the state of the art *at the time of Applicant's invention* (*e.g.*, without hindsight), did not teach, suggests or otherwise motivate the skilled person toward the presently claimed combinations. To the contrary, the state of the art would have guided a skilled person

wanting to explore combination therapy with one of these agents toward trying a combination *of either* AZD2171 *or* ZD1839 with a conventional, established *cytotoxic* agent, *but not with one another*. Since *actual circumstances* that existed at the time of the invention would have guided the skilled person *away* from Applicant's invention, it is both unnecessary and inappropriate for the Examiner to resort to an *artificial presumption* from *In re Kerkhoven* to assert a contrary result. Moreover, the relatively simple and predictable technology being addressed by the *Kerkhoven* court militates against its simplistic extrapolation to the far more complex technology involved in cancer therapy.

***Rejection of Claims 3, 4, 7, 8 and 15 - 35 USC § 103***

Claims 3, 7, 8, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herbst *et al*., Journal of Clinical Oncology, Vol 20, No 18, 2002: pp 3815-3825 (hereinafter "**Herbst**") in view of Galligioni *et al*., Lung Cancer 34 (2001) S3-S7 (hereinafter "**Galligioni**") and Malik *et al*., Targets, Vol. 2, No. 2 April 2003 pp 48-57 (hereinafter "**Malik**").

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Herbst, in view of Galligioni, Malik and Weichselbaum et al., US 6,420,335 (hereinafter "**Weichselbaum.**"

The Examiner asserts that **Herbst** teaches administration of ZD1839 (Iressa) to patients with non-small cell lung cancer, and also teaches that it is known in the art that non-small-cell lung cancer is related to high expression of EGFR, which promotes tumor growth. However, the Examiner correctly acknowledges that Herbst does not disclose the treatment of non-small cell lung cancer (NSCLC) with AZD2171.

The Examiner asserts that **Galligioni** discloses the treatment of non-small cell lung cancer with inhibitors of VEGF and VEGFR, and specifically points to reported studies on the clinical activity in non-small cell lung cancer of the synthetic tyrosine-kinase VEGFR-2 receptor inhibitor SU 5416. However, the Examiner correctly acknowledges that Galligioni does not disclose AZD2171 as a VEGFR inhibitor.

The Examiner asserts that **Malik** teaches AZD2171 as a VEGFR-2 inhibiting agent. However, the Examiner correctly acknowledges that Malik does not teach the combined treatment of AZD2171 with ZD1839 (Iressa) or the use of AZD2171 specifically for the treatment of non-small cell lung cancer.

With respect to claim 4, the Examiner cities Herbst, Galligioni and Malik as discussed above, but acknowledges that they do not teach the combination treatment with ionizing radiation. **Weichselbaum** is therefore cited as teaching treatment of cancers with a combination of anti-angiogenic compounds and ionizing radiation (pointing to claim 1), and noting as of particular interest that non-small cell lung cancer is noted at column 32, lines 45-48.

In combining these references in support of the rejection claims of 3, 7, 8 and 15, the Examiner asserts:

> First, one of ordinary skill in the art would recognize the ability to substitute the VEGFR-2 inhibitor of Galligioni with the VEGFR-2 inhibitor of Malik, where both compounds inhibit the same expression. for the treatment of non-small cell lung cancer.
>
> As such, one of ordinary skill in the art would then be motivated to have combined the agents of the primary and the teaching of the two secondary references in order to provide a third chemotherapeutic composition useful for the same purpose (treating non-small cell lung cancer). This position is consistent with well-established precedent holding that it is prima facie obvious to combine compositions known to be individually useful together so as to provide a third composition for the same use. See, e.g., In re Kerkhoven, 205 USPQ 1069, 1072 (CCPA 1980).

(Action at pages 3-4). With respect to claim 4, the Examiner further asserts:

> It would be obvious to one of ordinary skill in the art to substitute the anti-angiogenic compounds with other compounds known to treat the same cancer in the disclosed method of Weichselbaum et al, such as the combination discussed above.

(Action at page 5).

In short, it is understood that the Examiner's argument comes down to:

**Since**:

(1) Herbst teaches the use of ZD1839, an EGFR inhibitor, in the treatment of NSCLC; and

(2) Galligioni teaches the use of the VEGFR-2 inhibitor SU5415 in the treatment of NSCLC; and

(3) Malik teaches that AZD2171 is a VEGFR-2 inhibitor; and

(4) Weichselbaum teaches use of ionizing radiation with anti-angiogenic compounds (with reference to present claim 4);

**Therefore**, impliedly:

(a) AZD2171, as a VEGFR-2 inhibitor, could be substituted for SU5415 in the treatment of NSCLC; **and**

(b) Since the Examiner assumes that AZD2171 as well as ZD1839 can be used in the treatment of NSCLC, the "well-established precedent" of *In re Kerkhoven* automatically and without need for further analysis or discussion, *per se* creates a case of *prima facie* obviousness.

Applicant respectfully traverses this ground for rejection and the Examiner's reasoning in support thereof at several levels, as will be discussed further below. In summary:

(A) The applied references provide no suggestion or motivation for the presently claimed combined therapy of AZD2171 (a VEGFR-2 inhibitor) ***with*** ZD1839 (an EGFR inhibitor), but *rather teach away from* such a combination in favor of trying combinations of AZD2171 ***or*** ZD1839 with conventional *cytotoxic* drugs such as carboplatin, paclitaxel, gemcitabine and/or cisplatin, ***but not*** with one another.

(B) It is respectfully submitted that it is contrary to common sense and reason to mechanically extrapolate a presumption made in the context of combining spray dried detergents as involved in *Kerkhoven* to the combination of cancer therapies as here involved.

(C) Comparative evidence of record in the specification, and comparative clinical evidence published in the British Journal of Cancer (submitted with Applicant's response filed June 6, 2008) clearly demonstrate that the presently claimed combination therapy surprisingly and unexpectedly provides particularly significant and/or more than additive benefits relative to administration of either agent alone.

**(A) Herbst in combination with Galligioni and Malik (and/or Weichselbaum) Does Not Suggest but Rather Teaches Away From Combined Therapy of ZD1839 with AZD2171**

**Herbst** discloses phase I clinical trials of ZD1839 principally designed and conducted to assess the safety and tolerability of increasing doses of ZD1839 with patients with refractory solid tumors in cancer types associated with EGFR pathway activation, including NSCLC. The

only reference in Herbst to the use of ZD1839 in combination with any other therapeutic agent is in relation to a pilot trial of ZD1839 with the cytotoxic agents carboplatin/paclitaxel (see page 3824, 3rd paragraph). There certainly is nothing in Herbst to teach or suggest providing a combination of ZD1839 with another receptor tyrosine kinase inhibitor, let alone with an inhibitor of VEGFR such as AZD2171.

Accordingly, it is respectfully submitted that *if* it could be said that Herbst provides any suggestion for use of ZD1839 in combination therapy, Herbst would lead the skilled person toward combined therapy of ZD1839 with a conventional cytotoxic agent such as carboplatin/paclitaxel, and *away from* combined therapy of ZD1839 *with* a VEGFR inhibitor such as AZD2171, which is an entirely different type of agent.

**Galligioni** provides a review of angiogenesis and several anti-angiogenic agents in non-small-cell lung cancer. The Examiner has pointed specifically to the teaching in Galligioni in relation to the tyrosine kinase VEGFR-2 inhibitor SU5416 and the reports of its use in studies in non-small cell lung cancer. However, there is no mention in Galligioni of *either* ZD1839 or AZD2171, nor that AZD2171 is a VEGFR inhibitor. Rather, this reference is relied upon solely for its teaching that SU5416 is a VEGFR-2 inhibitor, and that it is used in non-small cell lung cancer. However, it is noteworthy that Galligioni also discloses that SU5416 has been used in combination therapy, but with the cytotoxic agents gemcitabine or cisplatin (see page S5, 2nd column), and more generally suggests the use of anti-angiogenesis agents in association or combined with established cytotoxic drugs (see page S6, 2nd column).

Accordingly, it is respectfully submitted that *if* it could be said that Galligioni provides any suggestion for use of the VEGFR-2 inhibitor SU5416 in combined therapy, Galligioni would lead the skilled person toward combined therapy with a conventional cytotoxic agent such as gemcitabine or cisplatin and *away from* combined therapy with an EGFR inhibitor such as ZD1839, which is an entirely different type of agent.

**Malik** provides a rather general review of VEGF as a target in the treatment of cancer and discloses AZD2171 as one of several inhibitors of VEGF (see page 54, 3rd paragraph). Malik mentions combination therapy briefly (see page 51, 3rd paragraph and page 55, 7th paragraph), but does not suggest any specific agents for combination with VEGF inhibitors, let alone for combination specifically with AZD2171.

**Weichselbaum** discloses use of an anti-angiogenic protein factor (angiostatin or endostatin) to sensitize tumor cells (including NSCLC) followed by administration of ionizing radiation. Only *biological* anti-angiogenic factors are disclosed, whose activity is quite different to that of small-molecule inhibitors such as AZD2171. Moreover, there is no mention of EGFR inhibitors or specifically of ZD1839, no less the combination of ZD1839 with an anti-angiogenic agent or with ionizing radiation. It should be born in mind that that the invention of independent claim 3 and independent claim 4 are both, first and foremost, combined therapy with *both* AZD2171 *and* ZD1839, and claim 4 adds ionizing radiation to that double combination. Weichselbaum provides no suggestion or motivation to combine AZD2171 *and* ZD1839, with or without ionizing radiation.

In summary, as is apparent from the above analysis of these documents, the only teaching in these cited documents in relation to combinations is directed to the combination of ZD1839 with a *conventional cytotoxic drug* such as carboplatin/paclitaxel; or the combination of an anti-angiogenesis drug (such as SU5416) with an *established cytotoxic* drug such as gemcitabine or cisplatin; or the combination of an anti-angiogenic factor protein with ionizing radiation. There is no teaching in any of Herbst, Galligioni, Malik or Weichselbaum to combine a VEGFR inhibitor with an EGFR inhibitor in the treatment of cancer, no less the specific combination therapy as presently claimed, being the administration of the VEGFR inhibitor AZD2171 with the EGFR inhibitor ZD1839, both of which are very different to that of conventional or established cytotoxic drugs, such as carboplatin, paclitaxel, gemcitabine or cisplatin.

It is therefore understandable that the Examiner has not asserted that these documents *per se* provide a teaching, suggestion or motivation to administer the presently claimed combination therapy. Instead, the Examiner bases the assertion of *prima facie* obviousness on a **presumption** that is said to arise from 1980 decision in *In re Kerkhoven*. The inapplicability of *In re Kerkhoven* will be discussed below. Nevertheless, it is respectfully submitted that such a presumption only applies if there is an absence of any *actual* teaching, motivation or suggestion to the contrary. Therefore, in view of the above analysis of these references, a person skilled in this art would be lead away from the presently claimed combination therapy by the express teachings of these references for combinations of *either* a VEGFR inhibitor such as AZD2171 *or* an EGFR inhibitor such as ZD1839 with a conventional established cytotoxic agent, *rather than*

*with one another*. Because there is an *actual* teaching, motivation or suggestion in the references *per se* leading one *away* from these combinations, there is no need to resort to any *presumption*, such as the presumption said to arise from *In re Kerkhoven*.

Therefore, it is respectfully submitted that no case of *prima facie* obviousness has been established by the Examiner, and this ground for rejection should be withdrawn.

**(B) Such Mechanistic Application of *In re Kerkhoven* To the Far More Complex Field of Cancer Therapy is Contrary to Common Sense and Reason**

The Examiner cites *In re Kerkhoven*, 205 USPQ 1069, 1072 (CCPA 1980) in support of the assertion that "one of ordinary skill in the art would be motivated to have combined the agents of the primary and teaching of the two secondary references in order to provide a third chemotherapeutic composition useful for the same purpose (treating non-small cell lung cancer).[1] The Examiner paraphrases from *Kerkhoven*, asserting "it is prima facie obvious to combine compositions known to be individually useful together so as to provide a third composition for the same use." (Action at page 4). This assertion, however, extends *Kerkhoven* well beyond its actual holding. *Kerkhoven* involved a process for the mixing of two conventional spray-dry detergents using a known method for mixing spray-dry detergent, which was held to be obvious. Applicant respectfully submits that the reasoning leading to holding in *In re Kerkhoven*, decided on facts relating to mixing spray-dried detergents, is not applicable to the present claims involving combinations of far more complex and unpredictable cancer therapy.

It is further submitted that such a mechanical application of *In re Kerkhoven* contravenes the intent of the Supreme Court in castigating "rigorous application" of the teaching, suggestion, or motivation (TSM) test. As the Federal Circuit recently explained in *Ortho-McNeil v. Mylan*, 86 USPQ2d 1196 (Fed. Cir. 2008), noting:

> In *KSR*, the Supreme Court explained that a "rigid" TSM test "is incompatible with our precedents." *KSR*, 127 S. Ct. at 1741. Mylan thus contends that the district court erred by rigorously applying the TSM test. The Supreme Court explained its reason for castigating a "rigid" TSM test: "The obviousness analysis cannot

[1] With respect to the Examiner's characterization of *Kerkhoven* as being "well established precedent," as best the undersigned can determine, this 1980 CCPA decision has not been applied or even cited on this point by either the CCPA or its successor Court of Appeals for the Federal Circuit in the over 28 years since that decision.

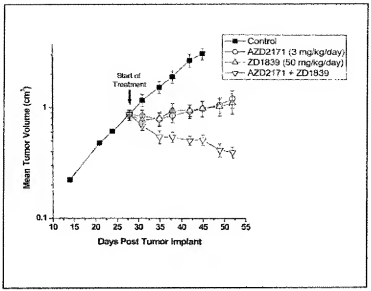
> be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents." Id. Indeed a rigid requirement of reliance on written prior art or patent references would, as the Supreme Court noted, unduly confine the use of the knowledge and creativity within the grasp of an ordinarily skilled artisan. Id. at 1742.

(86 USPQ2d at 1201-02; emphasis added). By application of the same reasoning, it is respectfully submitted that the mechanical application of the presumption of *In re Kerkhoven* to all combinations, without regard to the complexity or predictability of the involved technology, improperly confines the obviousness analysis to a formalistic concept, leaving no room for application of reason, logic or the actual state of the involved art.

**(C) Comparative Evidence Of Record Clearly Demonstrates That The Presently Claimed Combined Therapy Provides Significant Benefits As Compared To Administration Of Either Agent Alone**

*Even if* the combination of references were somehow deemed to give rise to *prima facie* obviousness, it is respectfully submitted that any such *prima facie* obviousness is overcome by the very significant benefits demonstrated to result from administration of the combined therapy compared to the administration of either agent alone, which results are more than additive and unexpected.

First of all, the data in the present application shows a clear improvement in activity over that provided by either agent alone. The first set of data presented at specification page 17, line 13 through page 18, line 12 and tabulated in Table I, was developed from human A431 vulval carcinoma tumour xenografts in nude mice. As graphically depicted in Figure 1, this data demonstrates a greater inhibition of tumour growth with the combination of AZD2171 and ZD1839 than with either agent used alone.




In fact, as is apparent from Figure I and reported under Table I, in contrast to treatment with AZD2171 or ZD1839 alone, regression was induced in all A431 vulval carcinoma xenografts treated with the combination of AZD2171 and ZD1839. The magnitude of this tumour regression (relative to the pre-treatment tumour volume on day 28) reached approximately 55% by the end of the experiment on day 52. Such a comparative result clearly supports the conclusion reached at page 4, lines 1-4 that it was truly *unexpected and surprising* that the particular compound AZD2171 used in combination with the particular compound ZD1839 produces tumour regression, being a significantly better anti-tumour effect than each of AZD2171 and ZD1839 used alone.

The second set of data presented at specification page 18, line 14 through page 19, line 19 was developed in a MMTV-neu transgenic model. As reported at page 19, lines 12-18,

- treatment with AZD2171 alone (at a dose of either 1 or 3 mg/kg/day) inhibited the growth of established MMTV-neu tumours significantly;
- treatment with ZD1839 alone (at a dose of 50 mg/kg/day *did not inhibit* MMTV-neu tumour growth;
- *but nonetheless*, the combination of AZD2171 (at a dose of either 1 or 3 mg/kg/day) with ZD1839 (at a dose of 50 mg/kg/day) *did produce greater inhibition* than either the respective dose of AZD2171 alone (at 1 or 3 mg/kg/day) or ZD1839 alson (at 50 mg/kg/day).

Again, it is respectfully submitted that this comparative result also clearly supports and confirms that the combination therapy of AZD2171 and ZD1839 produces an unexpected and surprising result, as stated and demonstrated by comparative data presented in the specification.

The Examiner is respectfully reminded that, although *conclusory statements* in the specification cannot constitute evidence of unexpected results, a specification *that provides data demonstrating improved properties* can establish unexpected results without need for such data to be repeated in a separate declaration. The Federal Circuit recently so held in *Sud-Chemie Inc. v. Multisorb Technologies Inc.*, 89 USPQ2d 1768 (Fed. Cir. 2008):

> Multisorb is correct that conclusory statements in a patent's specification cannot constitute evidence of unexpected results in the absence of factual support. See *In re Soni*, 54 F.3d 746, 750 [34 USPQ2d 1684] (Fed. Cir. 1995). However, the '942 patent provides evidence pertaining to the allegedly unexpected advantages of uncoated over coated films beyond its mere declaration that the results were surprising. Examples 1 and 2 of the '942 patent describe embodiments of the desiccant container in which uncoated but compatible laminate and microporous films formed seals with an average strength of more than nine pounds per square inch. In contrast, Example 3 shows that coated but incompatible films produced weaker bonds with a seal strength of only 2.77 pounds per square inch. The specification therefore contains specific evidence pertinent to Süd-Chemie's contention that the use of uncoated films yields advantages over more conventional combinations such as the incompatible surfaces disclosed in the Komatsu patent. See *Soni*, 54 F.3d at 750 (specification contained more than a merely conclusory assertion of unexpected results because it also provided data demonstrating improved properties).

(89 USPQ2d at 1774; emphasis added).

Therefore, it is submitted that a showing of significant and unexpected beneficial results of the claimed combination over the individual components has been established, sufficient to overcome any *prima facie* obviousness that might be implied from the presumption of *In re Kerkhoven*.

The Examiner's attention is also drawn to the paper by Bozec et al., *Br. J. Cancer* 97. 65-72. Dual inhibition of EGFR ad VEGFR pathways in combination with irradiation: antitumour supra-additive effects on human head and neck cancer xenografts (British Journal of Cancer (2007) 97, 65-72) (hereinafter "**Bozec**"). A copy of this paper was submitted with (attached to) Applicant's response filed June 6, 2008.

Bozec investigated the effects of combining treatments with AZD2171 and ZD1839, optionally also with irradiation, on human head and neck cancer xenografts. Relative to what would be expected from the combinations, Bozec found "supra-additive" effects from both the double combination of AZD2171 with ZD1839 and the triple combination of AZD2171 with ZD1839, also including irradiation. Bozec explains at page 66, paragraph bridging 1st and 2nd columns, how it evaluated whether the results from the combinations were "supra-additive" relative to what would be expected from results of treatment with the individual components:

> The effect of AZD2171 and gefitinib [ZD1839] alone or in combination with RT [irradiation] on tumour growth was evaluated. ... Evaluation of the effects on tumour growth consisted in measuring, for all groups, the mean tumour volume at the end of the observation period for the controls (day 30), when tumours in this group reached the average volume of 2500 $mm^3$ (maximal ethically acceptable volume). Fractional tumour volume (FTV) for each treatment group was calculated as the ratio between the mean tumour volumes of treated and untreated animals. This was performed for treatment a (FTVa), for treatment b (FTVb) and for treatment a + b (FTV a + b). The expected FTV for the a + b combination was defined as FTVa observed x FTVb observed. The ratio FTVa + b expected/FTVa + b observed was the combination ratio (CR). If CR> 1, there are supra-additive effects and if CR< 1 infra-additive ones. Strictly additive effects were observed if CR = 1.

(Bozec at 66; emphasis added).

Under the "Results" section on page 67, Bozec discussed the effects of AZD2171 in combination with gefitinib (ZD1839) and radiation on tumour growth and concluded:

> Antitumour effects for AZD2171 + gefitinib in combination were supra-additive (CR = 1.6) as were those for the triple combination of both drugs administered with RT (CR = 2). These CR values (>1) are consistent with tumour growth inhibition observed with each regimen.

(Bozec at 67; emphasis added).

Bozec thus adds further demonstration and confirmation of the unexpected "supra-additive" results achieved by administration of the presently claimed combinations relative to each component administered alone.

It is therefore respectfully submitted that *even if* the combination of references applied to the present rejection is somehow deemed to give rise to *prima facie* obviousness, any such *prima facie* obviousness has been overcome by the *demonstration* of unexpected results from

administration of the claimed combinations set forth in the specification itself. This unexpected result is confirmed by the further demonstration of "supra-additive" results arising from the claimed combinations and reported by Bozec in the prestigious British Journal of Cancer.

***Updated Table of Technically Related Pending Applications of Applicant's Assignee***

The Examiner's attention is drawn to the following *update* of the tables of co-pending U.S. non-provisional applications of Applicant's assignees which disclose and claim combination therapy including *either* AZD2171 *or* ZD1839, which table was earlier provided with Applicant's Amendment and Response of June 6, 2008. No additional documents are cited and therefore no further Information Disclosure Statement is required.

The following table lists such applications including AZD2171:

| US Appln | Date US Filed | US Pub. # | PCT Pub. # | Combination with | Current Status |
|---|---|---|---|---|---|
| 10/240,413 | 01 Oct 2002 | 20030144298 31 Jul 2003 | WO2001/74360 10 Oct 2001 | Anti-hypertensive | Assigned to Examiner Charlesworth E. Rae in GAU 1611; Final Rejection Mailed 10-03-2008. |
| 10/563,440 | 05 Jan 2006 | 20060160775 20 Jul 2006 | WO 2005/004871 20 Jan 2005 | ZD6126 | Abandoned. |
| 10/594,235 | 25 Sep 2006 | 20080113039 15 May 2008 | WO 2005/092384 06 Oct 2005 | Platinum anti-tumor agent, optionally IR | Assigned to Examiner Sharmila Gollamudi Landau in GAU 1611; Non Final Action Mailed 10-03-2008. |
| 10/594,233 | 25 Sep 2006 | 20080125447 29 May 2008 | WO 2005/092303 06 Oct 2005 | CPT-11 and/or 5-FU | Assigned to Examiner Sharmila Gollamudi Landau in GAU 1611; Non Final Action Mailed 10-29-2008. |
| 10/594,234 | 25 Sep 2006 | 20070135462 14 June 2007 | WO 2005/092385 06 Oct 2005 | Taxane. optionally IR | Assigned to Examiner Charlesworth E. Rae in GAU 1611; Response to Non-Final Office Action Entered and Forwarded to Examiner 01-14-2009. |
| 11/663,912 | 27 Mar 2007 | 20080015205 17 Jan 2008 | WO 2006/035203 06 Apr 2006 | Imatinib [Gleevec] | Assigned to Examiner James D. Anderson in GAU 1614; Non Final Action Mailed 09-22-2008. |
| 11/994,824 | 04 Jan 2008 | | WO 2007/003933 11 Jan 2007 | Gemcitabine [Gemzar] | Application Undergoing Preexam Processing; Not yet assigned or published |

The following table lists such applications including ZD1839:

| US Appln | Date US Filed | US Pub. # | PCT Pub. # | Combination | Current Status |
|---|---|---|---|---|---|
| 10/511,744 | 18 Oct 2004 | 20050215530<br>29 Sep 2005 | WO 03/088971<br>30 Oct 2003 | ZD6126 | Abandoned. |
| 10/523,838 | 08 Feb 2005 | 20050245549<br>03 Nov 2005 | WO 2004/014426<br>19 Feb 2004 | ZD6474 | Assigned to Examiner Christopher R. Stone in GAU 1614; Notice of Appeal Filed 01-12-2009. |
| 10/530,794 | 08 Apr 2005 | 20060122180<br>08 Jun 2006 | WO 2004/035057<br>29 Apr 2004 | AZD4054 | Assigned to Examiner Marcos L. Sznaidman; Response after Final Action Forwarded to Examiner 02-28-2009. |
| 11/597,940 | 29 Nov 2006 | 20070254893<br>01 Nov 2007 | WO 2005/117888<br>15 Dec 2005 | AZD0530 | Assigned to Examiner Paul E. Zarek in GAU 1617; Docketed New Case - Ready for Examination. |

***Conclusion***

All grounds for rejection have been addressed and, it is believed, overcome. In particular, it is respectfully submitted that the above discussion and legal arguments establish that *prima facie* obviousness has not been established by the references applied to this rejection, and *even if* it is deemed that *prima facie* obviousness has been shown, such *prima facie* obviousness has been overcome by the above demonstration of unexpected results achieved by the claimed combinations relative to the closest prior art. Accordingly, it is believed that all claims are now in condition for allowance, and a Notice to that effect is respectfully requested.

**EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
**Morgan Lewis & Bockius LLP**

Date: **March 10, 2010** By: _____

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